

Ready, steady, go! A two-part switch that regulates gene expression

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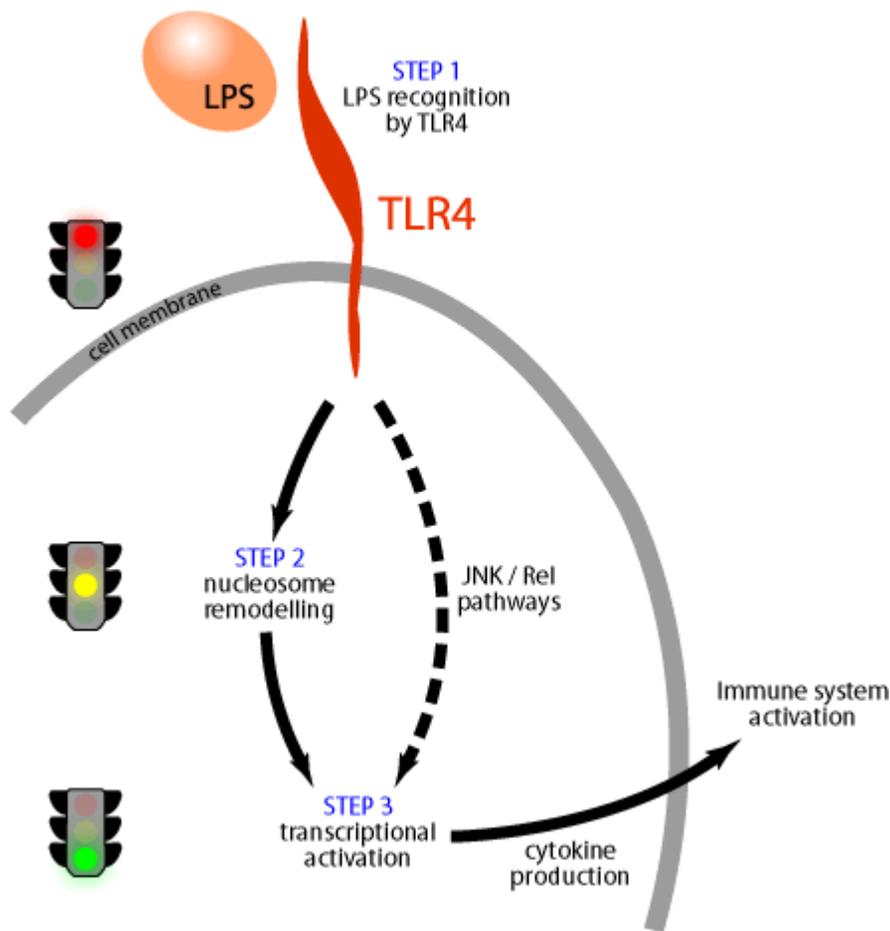
Traffic lights regulate the movement of vehicles on roads by transmitting 'stop', 'get ready' and 'go' signals to drivers. Similarly, antigen-presenting cells use cytokines as stop and go signals for lymphocytes. But what's the switch that changes the signal? In the January issue of *Nature Immunology*, Amy Weinmann and colleagues describe a two-part switch for regulating transcription of a cytokine gene: one signalling pathway leads to chromatin remodelling, and a second, independent pathway activates transcription.

An important element in the initiation of inflammatory responses is the activation of macrophages, resulting in the production of pro-inflammatory cytokines such as interleukin 12 (IL-12), a heterodimeric protein comprising p40 [<http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=3593>] and p35 [<http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=3592>] subunits. Toll-like receptors (TLRs), which are expressed on macrophages, recognize microbial molecules and transmit signals that initiate transcription of cytokine genes; TLR4 recognizes the Gram-negative bacterial product lipopolysaccharide (LPS). TLRs use several signalling pathways, including the nuclear factor κ B (NF- κ B) and Jun N-terminal kinase pathways, to initiate gene transcription. Which of these pathways stimulates macrophages to produce IL-12?

Using restriction enzyme accessibility assays, Weinmann and colleagues found that TLR4 signalling in response to LPS activation results in nucleosome remodelling at the p40 promoter. Curiously, although active NF- κ B is essential for transcription of p40, remodelling was not dependent on NF- κ B or another transcription factor, CCAAT enhancer-binding protein β . It seems that other TLR4-inducible factors can stimulate remodelling, perhaps making the p40 promoter more accessible to transcription factors such as NF- κ B.

So chromatin remodelling — a previously unrecognized endpoint of TLR signalling — behaves like an amber signal that prepares the chromatin for NF- κ B, the green light for transcription of p40. But what is the identity of the protein that recruits the remodelling complex, and what exactly is this complex? Further work in this area should enhance our understanding of TLR signalling and the regulatory mechanisms controlling induction of the inflammatory response.

Story by Elaine Bell, [Nature Reviews Molecular Cell Biology](http://www.nature.com/nrm/) [<http://www.nature.com/nrm/>]



TLR4 signalling pathway Activation of IL-12 subunit p40 transcription involves several coordinated steps. In the first step, Toll-like receptor 4 (TLR4) recognizes the bacterial surface molecule lipopolysaccharide (LPS). TLR4 then triggers the p40 nucleosome to undergo a remodelling event that is directed by an as yet unknown factor. TLR4 also activates other pathways such as Rel and JNK which act upon the remodelled nucleosome in the third step. This series of events provides a "green light" that allows the transcription of the IL-12 p40 gene to take place. The cytokine IL-12 is an important regulator of immune functions such as inflammation and Th1 development.

Important Links

Live PubMed searches

- (1) Regulation by nucleosomes
- (2) Toll-like receptor 4
- (3) REVIEWS

Additional NCBI resources

TLRs in Locus link [http://www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=tlr*&ORG=Hs]
 Homologene
 TLR4 in OMIM

Box: Use BLAST to search for TLR4

Click on the link below to start an html tutorial.

Blast the human genome with mouse TLR4 [http://www.ncbi.nlm.nih.gov/Coffeebreak/CB19_TLR/gene1.html]